REMARKS

In response to the Notice of Non-Compliant Amendments, Applicants present herein a complete listing of all of the claims along with a proper status identifier in ascending order. The substance of the Amendment filed on November 26, 2003 is reiterated herein.

Claims 1-76 were pending in the instant application. Claims 3, 6, 12-16, 18-21, 24, 28-31, 33, 34, 38, 40-47, and 52 have been cancelled, without prejudice, as being drawn to a non-elected invention. Claims 1, 2, 5, 8-11, 17, 26, 27, 32, 36, 37, 39, and 50-51 have been amended. Claims 4, 6, 7, 22, 23, 32, 35, 38, 48-49 and 54-76 have been cancelled, without prejudice. Therefore, claims 1, 2, 5, 8-11, 17, 25-27, 36-37, 39, 50-51, and 53 are pending in the application.

Support for the amendments to the claims can be found throughout the specification and claims as originally filed. No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or in one or more separate applications.

Election/Restriction

In view of the finality of the restriction requirement and Applicants' election, claims 3, 6, 12-16, 18-21, 24, 28-31, 33, 34, 38, 40-47, and 52, which are currently withdrawn from consideration, have been cancelled without prejudice as directed to non-elected subject matter. Applicants hereby reserve the right to pursue the non-elected subject matter of the cancelled claims in one or more divisional applications.

Substitute Specification

The Examiner has objected to the substitute specification filed on August 16, 2002 in Paper number 12 because it does not confirm to 37 C.F.R. 1.125(b). Applicants state that the Substitute Specification filed on August 16, 2002 does not contain no new matter.

Drawings

Applicants note with appreciation the acceptance of the substitute drawings (Figures 1-4) filed April 5, 2001.

Claim Rejections

Nonstatutory Double Patenting Rejection

Claims 1, 2, 4, 5, 7-11, 17, 23, 25-27, 35-37, 39, 49-51, and 53 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 12, 16, 18-20, and 23 of U.S. Patent No. 6,100,042. In addition, claims 1, 2, 4, 5, 7-11, 17, 23, 25-27, 35-37, 39, 49-51 and 53 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 21, 23, 24, 26, 28, 29, 31, 32, 34, and 36 of U.S. Patent No. 5,789,184 or U.S. Patent No. 5,876,951. Applicants will file a terminal disclaimer if still rejected once the remaining claims being held otherwise allowable by the Examiner.

Rejection of Claims 22, 32, and 48 Under 35 U.S.C. §101

The Examiner has rejected claims 22, 32, and 48 under 35 U.S.C. §101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. The Office Action at page 8 indicates that "[s]ince an orphan cell surface receptor has no known ligand and is not necessarily linked to any known biological functions, any known diseases or medical conditions, there is no specific and substantial utility for an orphan cell surface receptor and thus for a mixture of recombinant yeast cells comprising the orphan cell surface receptor."

Applicants respectfully traverse this rejection and submit that the present invention has a *specific and substantial utility which is credible and well-established*; namely, ***the test polypeptides generated by the recombinant cells of the instant invention may be used to identify the polypeptides that react with orphan cell surface receptors*** . Thus, the pending claims provide a step in the process for the identification of the function of orphan cell surface receptors.

In short, the present invention provides a *substantial* utility in that the claimed mixture of recombinant cells are engineered to express an orphan cell surface receptor and are transformed with constructs that express numerous polypeptides. The recombinant cells of the invention also contain a detectable signal such that modulation of signal transduction activity of the orphan cell surface receptor, *i.e.*, reacting of the test polypeptide (ligand) with the orphan cell surface receptor, may be detected. The invention, therefore, provides a well-established utility in, for example, identifying the test polypeptides that react with orphan cell surface receptors so that the function of the orphan cell surface receptors may be determined.

Orphan receptors have been conserved in evolution and may thus be found throughout the human body. Clearly, orphan receptors are involved in important biological functions. By identifying ligands that bind to known orphan receptors, it may be possible to (1) determine the function of the orphan cell surface receptor and (2) use the orphan cell surface receptor as a drug target. However, it is not possible to exploit this opportunity to find new drug targets, unless one first determines the function of the orphan cell surface receptor.

The recombinant cells of the present invention may also provide valuable information about the ligand that activates the orphan cell surface receptor. In particular, by analyzing the polypeptide sequence of the ligand, one of ordinary skill in the art could readily determine the gene family of the ligand, thereby providing additional information about the orphan cell surface receptor that is activated by the ligand.

In view of the foregoing, it is evident that Applicants' invention has a *specific, substantial, credible and well-established utility* that would have been readily apparent to one of skill in the art. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. §101.

Rejection of Claims 22, 32, and 48 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 22, 32, and 48 under 35 U.S.C. §112, first paragraph "since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Applicants respectfully traverse the foregoing rejection. The teachings in the specification and the knowledge available to one of ordinary skill in the art at the time of filing

are sufficient to make the recombinant cells of the claimed invention. Applicants have provided working examples that disclose how to make and use the claimed recombinant cells of the instant invention.

Example 11, for example, teaches the identification of a ligand using expression of a random peptide library in yeast expressing the human thrombin receptor. In this example, experiments detailing the (1) establishment of a strain of yeast designed to express the human G protein-coupled receptor for thrombin; (2) expression of a random peptide library in the afore-mentioned strain of yeast and (3) activation of the endogenous yeast pheromone pathway upon stimulation of the thrombin receptor by peptides encoded by a random library expressed within the same strain of yeast are described.

In addition, Example 3 provides a working example that demonstrates a synthetic oligonucleotide encoding a peptide that is expressed so that the peptide is secreted or transported into the periplasm. Example 4 demonstrates the ability to engineer yeast such that they secrete or transport oligonucleotide-encoded peptides (in this case their pheromones) through the pathways normally used for the secretion or transport of endogenous pheromones. In addition, Example 5 demonstrates the utility of the autocrine system for the discovery of peptides which behave as functional pheromone analogues. This system can be used, by analogy, to discover peptides that productively interact with any pheromone receptor surrogates. In Example 6, Applicants teach several projected uses of the autocrine C5a strains, including the identification of compounds with therapeutic utility.

In view of all of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 U.S.C. §112, first paragraph.

Rejection of Claims 1, 2, 4, 5, 7-11, 22, 23, 25-27, 32, 35-37, 39, 48, 49-51, and 53 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1, 2, 4, 5, 7-11, 22, 23, 25-27, 32, 35-37, 39, 48, 49-51, and 53 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention. In particular, the Office Action indicates that the term "an expressible recombinant gene" is confusing and ambiguous as to whether the recombinant gene is operatively linked in a

functional manner. In addition, the Examiner is of the opinion that the term "a heterologous potential receptor effector polypeptide" is confusing with regard to "potential." The Office Action indicates further that the word "effector" has no specific or art accepted meaning. Lastly, the Office Action indicates that it is unclear how a "test polypeptide" is related to "a variegated population of receptor effector polypeptides" recited by the claims.

Applicants respectfully traverse the foregoing rejection. However, in the interest of expediting prosecution, and in no way conceding to the validity of the rejection, the instant claims have been amended such that they no longer recite these terms. Thus, Applicants respectfully request reconsideration and withdrawal of this section 112, second paragraph rejection.

Rejection of Claims 1, 2, 4, 5, 7-11, 22, 23, 25-27, 32, 35-37, 39, 48, 49-51, and 53 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1, 2, 4, 5, 7-11, 22, 23, 25-27, 32, 35-37, 39, 48, 49-51, and 53 under 35 U.S.C. §103(a) as being unpatentable over King *et al.* (Science 250:1210123, October 5, 1990) in view of Devlin *et al.* (Science 249:404-406, July 27, 1990), Scott *et al.* (Science 249:386-390, July 27, 1990), Cwirla *et al.* (Proc. Natl. Acad. Sci. USA, 87: 6378-6382, 1990), and Ladner *et al.* (U.S. Patent No. 5,096m815, March 17, 1992). According to the Examiner, King *et al.* teaches the construction of yeast cells that express a heterologous G protein-coupled receptor, a human β2-adrenergic receptor, and a heterologous Gα subunit of a G protein that placed the endogenous pheromone response pathway under the control of the heterologous receptor and a *lacZ* gene under the control of the pheromone responsive FUS1 gene promoter. However, ***King et al. does not teach or suggest the use of an autocrine system to identify specific polypeptides that react with orphan cell surface receptors***. In fact, the Examiner admits that King *et al.* fail to teach or suggest the pending claims wherein a yeast cell expresses a variegated population of test polypeptides to be tested endogenously. While King *et al.* describe a method for scoring growth arrest or β-galatosidase induction, thereby providing a way for testing the functional properties of mutant receptors using these yeast cells, it contains no teaching or suggestion regarding the expression of a variegated population of test polypeptides, as required by the claims. The failure of King *et al.* to teach or suggest the claimed autocrine system to identify

specific polypeptides that react with orphan cell surface receptors, leads to a failure of the reference to teach or suggest the claimed methods.

Devlin *et al.*, Scott *et al.*, Cwirla *et al.*, and Ladner *et al.* also do not teach or suggest the pending claims nor provide the elements missing from King *et al.* to teach or suggest the pending claims. While these references may teach the general concept of using a peptide library to identify ligands of receptors, none of the cited references teach or suggest, either alone or in combination, the use of an autocrine system to identify specific polypeptides that react with orphan cell surface receptors. In particular, they do not teach or suggest the claimed methods of the present invention, *i.e.*, a mixture of recombinant cells, each cell containing an expressible recombinant gene encoding a heterologous orphan cell surface receptor whose signal transduction activity is modulated by interaction with an extracellular signal; and an expressible recombinant gene encoding a heterologous test polypeptide, wherein collectively the mixture of cells expresses a variegated population of the test polypeptides, and modulation of the signal transduction activity of the receptor by a test polypeptide provides a detectable signal. Applicants therefore request withdrawal of this §103 rejection.

Claim Objections – Minor Informalities

The Examiner objects to claims 1, 2, 4, 5, 7-11, 22, 23, 25-27, 32, 35-37, 39, 49-51, and 53 because they recite unelected subject matter, *i.e.*, subject matter other than the elected subject matter of an orphan cell surface receptor. Further, the Examiner indicates that claims 10, 11, and 27 recite unelected subject matter pertaining to a detectable signal or a reporter gene. Applicants have amended the claim herein to conform to the elected subject matter. Therefore, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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